ANTIMICROBIAL RESISTANCE

PUBLIC MEETING

PRE-APPROVAL STUDIES AND PATHOGEN LOAD

BREAKOUT GROUP DISCUSSION - AQUATICS

THURSDAY, FEBRUARY 24, 2000

8:49 A.M.

DOUBLETREE INN

1750 Rockville Pike

Rockville, Maryland

Randolph Room

I N D E X

BREAKOUT GROUP DISCUSSION - AQUATICS

February 24, 2000

Keynote: "---" indicates an inaudible in the transcript.

BREAKOUT GROUP DISCUSSION - AQUATICS

(8:49 a.m.)

(All participants away from microphone.)

CHAIRMAN MacMILLAN: To get things going, I have prepared a little bit of a power point presentation to consider --- also prepared something you can take a look at. The way I approached this, I think it was late at night so -- and I haven't had a chance to really preview this but the way I approached it was trying to be as scientific and objective as I could, what criteria would we use.

(Slide.)

As an ivory towered scientist, what would I want to use in order to provide some --- sound scientific data to the FDA or anybody else --- to give the basic --- information, the probability of resistance transfer from the aquatic bacteria, whether it's --- pathogen or not --- a human bacterial pathogen. And if we could go to the next slide.

(Slide.)

So I happened to have with me a publication and that publication focuses in on what is sound science? What constitutes sound science? And they have a basic definition that says sound science --- described as organized investigations --- conducted by qualified personnel using document evidence and leading to verifiable results.

And to me, one of the key words there is verifiable

and that's a tough one for me, and understanding, I'm not a antimicrobial biologist or anything like that, but I am a scientist, or at least I used to be, before I got involved in business and -- but the key was verifiable results.

Now how can you plan something -- how can you design external protocols if you take from the aquaculture environment, all this bacteria and perhaps use of antibiotics -- or purposely use of antibiotics to do this experiment, we go all the way from there to the human bacteria?

Well --- design something like that. You can go to the next slide.

(Slide.)

I don't think our science is there yet to allow us to do that, so you look at alternatives. But in the meantime, you also look at -- and I looked at further at what sound science means in terms of data and conclusions. They are the use of scientific method, obviously.

Well, what's the scientific method? You have to have a chance to --- hypothesis and right now, we don't have the principal hypothesis because there's so many steps involved and we don't have the technology --- the research tools to go all the way from the beginning to the end.

We also use systematic --- experimental protocols and that's where a lot of the people yesterday were talking about, and the day before, was how do you provide --- and how come our

microbial studies won't be repeatable?

And one of the things that we talked about in aquaculture was, repeatability of our tests and very, very difficult to get --- whether it's drugs or any other type of research in aquaculture. One pond is so different than another pond, very, very difficult.

And even in the laboratory, it's difficult outside of --- yet repeatable results --- but in fish, it's very, very difficult to --- but you also have to have a hypothesis -- next slide.

(Slide.)

--- yet again, is spurred by results and, to me, again, the key was, one of the keys is is it repeatable and -- the next slide.

(Slide.)

I don't know that we have the wherewithal to do that yet. So, what does the scientific method help us to do? Well, again, the --- and for conclusions that are supported by the data --- what Kelly was talking about --- some way to tell her constituents that if you eat this food, whether it's seafood or anything else, it's going to be safe for you. You can't provide that.

I don't think the FDA can tell the American public that there's a hundred percent --- that if you --- that you're not going to get sick. There is some risk involved and there's

risk involved with --- so that's what she was after, I think, was that hundred percent guarantee.

I don't think anything we do, anything outside of the drug world, there's nothing that scientists can do to provide that hundred percent assurance that --- that it's safe. You just can't do that.

(Slide.)

So, in view of what was said yesterday, and Bill, I think you may have brought up from a realistic standpoint, the one thing you're going to be dealing with is in aquaculture is using basically hand-me-down drugs, antibiotics --- so I look at that as an advantage in ---

We really have an advantage. The antibiotic that's going to be used in aquaculture is going to be -- there's going to be a lot of history about that antibiotic --- so we're going to have -- we should know a lot of the circumstances that happened with regard to any particular drug and that's --- and I think that's what Meg was talking about yesterday.

The other --- in aquaculture is really quite small. In the whole scheme of things, we're really quite small and we're localized. --- the practice industry is localized in about three states in the deep south. --- industry and at this point --- a factor in antibiotics in trying to --- antibiotic ---

On salmon industry, we're small in the United States

--- I think it's really quite small, particularly compared to Canada and Europe.

(Slide.)

So we think that, or I think, I'm proposing really --- class III drugs, whatever --- drugs are considered in aquaculture. And the reason for that is that a drug company -- drug companies, they're going to put their higher cost drugs into an animal industry that's going to, if it's much larger than aquaculture.

And I don't know how it is at Schering-Plough, but probably get into consider aquaculture in the United States, I guess because we already have whatever drug is approved in other countries. Is that right? So you had a lot of data already.

But --- the most -- the drug company's not going to jeopardize an approval for aquaculture, working on an approval for aquaculture that's going to jeopardize a major --- just doesn't make financial sense to do that. And that's always been the problem or one of the problems in aquaculture in the United States.

Drug companies don't want to take -- there's not enough financial incentive in there for them to go ahead and try to get a drug approved from -- that's already approved in the major --- and try to get it approved in aquaculture.

It's just not financially -- one of the arguments has

been, well if we do that, we're going to have to open up our files to the FDA to take a look at --- and we don't want to jeopardize that. That's not something that we want to risk.

(Slide.)

So I went and thought, what are the drug approval needs for aquaculture application? Well, one of the first things is are there food-borne pathogens of concern? And then, the next question, that step-wise question, are there antibiotic resistant food-borne pathogens or antibiotic food-borne resistant pathogens of concern?

And then you start getting into the more difficult things to resolve --- environmental --- of an antibiotic, why --- adversely affects significant microbial flora. I think that's already part of the testing that a drug company has to do. Is that right?

DR. SIMMONS: From a microbial point of view, depends on how much -- it's not historically something that you look at. You look at the --- and the affect on --- organisms and things like that ---

(Simultaneous conversation.)

DR. SIMMONS: Looking at most -- I would say that the environmental --- of most of these ---

CHAIRMAN MacMILLAN: One of the things I remember is I was involved in --- research and I know that Abbott --- aquaculture --- I don't know if it was --- I know they looked

at changing microbial flora in a catfish pond and so I thought that was part of the normal approval process but I guess it's not.

DR. GOTTHARDT: There is an --- safety package ---

CHAIRMAN MacMILLAN: Okay.

DR. GOTTHARDT: I think that at this point, environmental --- so this is --- after hearing a little bit more about that ---

VOICE: Not sure that that's really been done in the past.

DR. GOTTHARDT: In the past, but I'm talking about as far as where we are now. That would be ---

CHAIRMAN MacMILLAN: The other question is, of course, if the microbial flora develops resistance, whether this pathogen --- or in the aquatic environment, if it develops resistance, can it go through what I call the cascade? --- and that's the one where I have some technical problems in figuring out how to get there.

So, I would suggest if there -- there really are some questions that we can answer, but others that can't be answered using scientific method. And the reasons for that suggestion is that ---

DR. BUTLER: I was going to say ---

CHAIRMAN MacMILLAN: The reason that we -- that there are some problems in --- in scientific method for some of these

things --- is that we really have a very rudimentary understanding of the resistance transfer mechanisms and particularly the probability of the resistance transfer --- we know what happens.

We don't know how often it happens, what environmental conditions --- that transfer. We also know that aquatic bacteria can be resistant to an antibiotic in the absence of an antibiotic and that's -- there's a problem there and --- what's the break point? I think we're getting to that --- the CCLS type of stuff, but a little ways away from that. Go the next one.

(Slide.)

So what's the --- of resistance transfer --- aquatic bacteria --- human pathogens. So we just don't know -- we don't have a good way to predict that and --- keeping in mind what the endpoint is, to try to answer the question, what is the --- of going from aquaculture antibiotic application to human pathogen --- a number of permutations that are different cascades if you can ---

So what I would suggest, or what I'm proposing -- and again, this is just a --- is that --- survey the aquaculture environment for human bacterial pathogens. We look for feces in the --- of those --- we know already that some aquaculture environments have a greater abundance of human pathogens --- particularly if the aquaculture -- this doesn't happen in the

United States as far as we know, but if they --- human waste --- into the pond or if you put the animal waste into the pond, or aquaculture environment, you're going to have a high prevalence of human pathogens.

And then I'd suggest that we do qualitative risk analysis. If we find, for example, that there's a large number of salmonella --- or listeria monocytogenes --- we can put that into a --- qualitative risk analysis. It's really difficult to quantitate some of this.

And then --- that initial qualitative risk analysis indicates a likely risk and a significant risk, and I don't know how to judge --- significant. But we can -- if we do some in vitro testing of the antibiotic resistance --- before and after the application of the proposed -- the antibiotic that we're trying to get approval for.

And then based on what -- the human --- is the in vitro testing is far more replicable than anything else that we have --- and so based on that study, we can advise our qualitative risk analysis to help us out in making a judgment.

So, I propose a kind of a --- this is something Wendy suggested, that it was a step-wise process of analysis, but I suggest that we -- we'll be looking mostly --- products ---

DR. SIMMONS: Randy, I'm going to challenge that.

CHAIRMAN MacMILLAN: Okay.

DR. SIMMONS: ---

CHAIRMAN MacMILLAN: Okay. That's fine. You're looking at class I products?

DR. SIMMONS: No.

CHAIRMAN MacMILLAN: Okay. The class II? I had a question mark about class II because I didn't know what was going on with that.

DR. GOTTHARDT: Randy, I'll chime in on that, too. ---

CHAIRMAN MacMILLAN: Okay. ---

DR. GOTTHARDT: Class III is --- in terms of ---

CHAIRMAN MacMILLAN: Okay. --- classify something like oxytet is a class III. It's class II?

DR. GOTTHARDT: I am probably not the best person to comment on that. --- would follow a class II.

CHAIRMAN MacMILLAN: Okay.

DR. SIMMONS: The other part that drives that --- for anything that's potentially consumed by humans, aquaculture obviously won't justify developing that pathogen if there are no other indications. So the only way you're going to justify that package is if you tag it onto another --- and that's going to ---

CHAIRMAN MacMILLAN: And part of my lapse there might be that I don't have a clear understanding of how to categorize the drug, class I, II or III, and I apologize for that. But the same thought process will go along, either it's class II or

III.

But we do know that temperature, water temperature, has a major impact on the kinds of bacteria that are likely to show up in the aquatic environment and certainly the growth characteristics of those bacteria, we do have some scientific knowledge about that.

So, I suggest we go one of two ways -- we make a --- decision about whether it's a warm water or a cold water application and whether it's a freshwater or saltwater application.

And once that happens, if you identify some potential food-borne human pathogens to be concerned about. In the warm water case, actually all cases, --- use --- probably is present and something we need to look at. Salmonella is present, we know, in both salt and freshwater, warm water climates. Here, I'm not sure ---

I can tell you in my particular situation, you don't find salmonella and you --- it's a real unique --- situation where there is water coming right out of the --- and goes right from the --- to our production units so far, and so we're not likely to have salmonella. --- have a terrestrial animal --- mammal around, they're not likely to get anything like that.

But in our particular case --- there are some --- that use irrigation water in their production and those farms --- do have salmonella because they have -- because they don't

know where the water's coming from, basically, and there is a big area --- so it's possible to have some --- salmonella foods doing anything --- producing, I don't know so we need to take a look.

And then in saltwater cases in cold temperatures, we need to look at vibrio and so, those would be some human pathogens, food-borne type pathogens that we could look at.

So the result of the risk analysis -- the next one.

(Slide.)

I think we can identify the rate of resistance of food-borne pathogens for aquaculture. I think we can get that. Just how strong that analysis will be, I don't know. We'd have to go through and exercise that way to judge that.

DR. REINSCHUESSA: --- the rate ---

CHAIRMAN MacMILLAN: Rate of resistance. This would be prevalent --- the extent of resistance --- we may not have been --- I just --- anyway that based on that information we get, we get the prevalence of food-borne pathogens for aquaculture products and some measure then of resistance of those food-borne pathogens, you could get at --- next one.

(Slide.)

And then I suggested that we have some post-approval monitoring on seafoods and if we find bacteria, human --- bacteria, we would check those for resistance to --- antibiotics.

The problem with that is that the post-approval monitoring, you don't know where that bacteria came from. It could be salmonella. You don't know where that salmonella came from --- the processing of the product or if it came from the aquaculture facility itself. We don't know that so that's a weakness to the post-approval but it's a step.

As long as people keep things in perspective, then they can work with that and maybe they'd ultimately lead us to ask some more germane questions or questions that we could -- that are actually --- next one.

(Slide.)

So the question is deferred because, to my view, we don't have the tools we need to go all the way. What is the probability of human pathogenic bacteria? What is --- develop resistance as a result of an aquaculture application of an antibiotic? Next question.

(Slide.)

From my perspective, we just don't have the tools to show cause and effect and again, the post-approval monitoring might give insight. Next.

(Slide.)

Consequences, and this, Kelly, I was trying to address some of your concern which you voiced yesterday. This will be what I would be willing to say, based on that analysis. I'm not a regulatory person and I am certainly biased because

I'm industry.

But I felt that --- also in charge of quality assurance in food safety and I would have no qualms at all about making the statement such as that. I probably wouldn't include the very last sentence because that's just not a good statement to make to --- informed public but I just put that in there because we can't provide absolute assurance. You can't do that in anything.

DR. BUTLER: Well, I was just wondering if I could comment. I was just trying to ask if I could comment during the piece because going back on the other site, you said in post-approval monitoring, you could look at -- sorry, it's --- post-approving monitoring you had said -- I guess maybe it's one before that -- sorry.

That you could look at human pathogenic bacteria but you couldn't be sure where they came from which I think is the point of the pre-approval where you do it in a contained environment to say does this drug cause antimicrobial resistance and it doesn't -- as we said yesterday, it doesn't necessarily have to be a human bacterial pathogen but whatever, does it cause antimicrobial resistance in a bacterium?

And in the controlled pre-approval study, which is why I think people are looking for pre-approval information, if you know, yes, it is going to cause it sooner or later but if you know the mechanism or if you know that it's not causing

important cross resistance, then you can say, well there, we did our pre-approval in a controlled setting.

There is some resistance for this. There is apparently no cross resistance; therefore, there's some assurance for someone who would be using it in aquaculture to take it the next step down the line to say, we are not contributing to any problem with antimicrobial resistance that might be turning up in the water that you're swimming in and the water you're drinking.

So, that's the piece that I see important being said because what you said in that later paragraph, and further on in the last one, we can say that -- sorry, the next one -- the next consequence is yeah, based on careful risk analysis, etcetera, so you couldn't -- at this point, you don't know.

That's what the point of the pre-approval is, is to say if we do this, does that result? And if we can say, okay, we tried it in this situation. It didn't show anything to my knowledge.

It's not causing an important cross resistance or it's not apparently causing antimicrobial resistance, you know, in the short term at least in that period of time that we did our study. And probably, as I said, the cross resistance is a bigger issue. But I mean --

DR. REINSCHUESSA: Okay. I want to star your comments ---

DR. BUTLER: Sure.

DR. REINSCHUESSA: But, in a way, I think you're looking at the pre-approval studies with rose colored glasses because --- find resistance developing in --- cross resistance development and I think the pre-approval, the most we can hope for is ways in dealing with that --- not going to be able to use it as a plan to say this is safe.

DR. BUTLER: No, I would never expect that, but what we want to know is what we're dealing with.

DR. REINSCHUESSA: Right.

DR. BUTLER: And you're right; in some cases --

DR. REINSCHUESSA: But it's not going to be a weapon for you to say my stuff is ---

DR. BUTLER: No.

DR. REINSCHUESSA: And the antimicrobials are going --- but you know, what I would hope, you know, sort of going back to the --- in a pre-approval process is to be --- to develop tools that are used --- for change management practices on farms when they see those changes that we predicted from the ---

DR. BUTLER: And those are important as well, but no, not -- I am not suggesting, as I say -- using them is going to cause antimicrobial resistance but I think identifying cross resistance is a very important one to say, well, we did look at that but we haven't got any evidence that.

There's no such thing as safe anything, but you have to -- if you see that the antimicrobial cross resistance is an issue, which I think it is, then we can say we have looked at it.

And there's no such thing as safe anything but there are things that we know that we have to address and I think that would be one. But the additional information is useful as well. How can we address antimicrobial resistance, short of course, high dose, all of those things to mitigate the effects.

CHAIRMAN MacMILLAN: Okay. Well, Renada also prepared some power point slides if you want to go to that.

DR. SIMMONS: I need to go back to yours, just one more. I have a lot of problems with the qualitative risk assessment and the reason for that is what's been tried already and there's major, major issues with how you go about that --- put into that.

I am in full agreement that there should be a risk assessment provided and the risk assessment based on the correlation of the antibiotic to a human antibiotic at the same class or in the same --- with looking at mutation frequencies.

That's certainly a guide to tell you what you can expect and I have no problem with looking at making those --- as well as mechanism of resistance and then you, from that, that is your risk assessment.

We feel this poses no risk because of the following reasons or it does pose risk and the following steps should be looked at and that's where you would go with -- a qualitative risk analysis, I have no idea how you would even -- what you would even put in for that.

CHAIRMAN MacMILLAN: And a lot of your qualitative was that it was just --- not all of the scientific information that you would like to have in order to make a quantitative risk assessment. So by default --- it's a judgment that has to be made --- assessment of --- but --

DR. SIMMONS: You could be talking the same thing.

CHAIRMAN MacMILLAN: Well, it could be, but nevertheless, we'll have to --- so as a drug company person, you would agree to a risk assessment as some sort of -- the risk assessments that you do --- a hybrid of --- some quantitative information.

DR. SIMMONS: We used the Framework document.

CHAIRMAN MacMILLAN: Okay.

DR. SIMMONS: Okay.

CHAIRMAN MacMILLAN: Okay.

DR. REINSCHUESSA: I sort of looked at some of the questions that they were asking us to --- I just --- different things to consider --- pre-approval studies. One thing we really didn't talk about much is --- systems and use of antimicrobial bacteria that could come from other sources.

You talked about salmonella --- not only from aquaculture --- and so, resistance can come from all those animals as well and not be --- to aquaculture. So those are just other things that we should consider, including chemicals and metals -- sometimes water content --- more heavy metal that may or may not be, you know, at a level where it's not toxic to the animals --- changing profiles --- so that was one more thing.

The model bacteria, if you want to use a model for your study, I sort of picked out what I thought and this is from and this is for people to add onto --- thinking about it. You want to have abundance --- fish in the water and --- easy to grow and characterize which may not be realistic for some of the pathogens for humans, representative of what's occurring the production --- and is not currently resistant to the test drug or other --- and you were saying, well just pick a drug or pick a bug --

DR. BUTLER: Oh, to start with. That's what I'm saying.

DR. REINSCHUESSA: And I'm trying to --

DR. BUTLER: I'm not telling you to pick one.

DR. REINSCHUESSA: Right.

DR. BUTLER: I'm saying they know which bug is in which species, so I --

DR. REINSCHUESSA: But the problem is -- I mean, I'm

looking at what I used in the past as clinical data when we've had --- fish across my plate and --

DR. BUTLER: As it were.

DR. REINSCHUESSA: You know, I thought, well, okay, --- is everywhere. You know, it's in the water. It's in the fish and it's on every freshwater --- I mean, every clinical --- I've come across has been resistant to oxytet and to sulfas. So in trying to figure out what bug we want to use --

DR. BUTLER: Sort of push us to the in vitro versus which is what you were saying, it pushes you more to doing a study in an in vitro setting where you have to use sort of a -- if there's such a thing in fish, specific pathogen free fish and then introduce the bacterium which is just normal and --

DR. REINSCHUESSA: Is it relevant to what's out there?

DR. BUTLER: Oh, well I'm talking about the effect of drugs, specifically, and what we're trying to get at is the effect of using an antimicrobial. Is it relevant? What you're saying is true. All of that is out there. What we're trying to assess is what is the impact of a particular medication? Is it causing a difference, yes or no? It's a tough question to ask but it pushes the question more into a laboratory, more into a controlled environment, as you say.

DR. SIMMONS: But I think you hit on -- there's three things that were brought out yesterday. Number one, is it

relevant? Number two, is it predictive? And number three, can it be validated? And if it doesn't pass those, I wouldn't touch it; I wouldn't recommend it. That's a real issue.

DR. REINSCHUESSA: you know, the three things that you mentioned --- okay, so what is our goal for doing a pre-approval test and I think mine are to develop those little strategies, compare it with what you find in your post-market surveillance in the target --- fish pathogen and also --- that we hopefully will come up with on slide one, or slide two, you know. And then change drug use if needed.

Now, Meg brought in an important point --- to switch, and we need more drugs to switch, but I mean, that would be one thing that, you know, the post-market surveillance would have been --- and then, you know, just sort of --- because there are things that simply live on farms and if you have an indicator or --- there are things that can start the investigative, if we do have single organisms telling us ---

So that's where I would say okay, maybe pre-market --- come up with some strategies for --- and so right now, we don't have --- and, you know, I'd really like to see more effort on the major species than on the minor species for these kind of pre-market studies.

(Slide.)

I guess this is my push, to try to get one drug --- I think they're important in terms of resistance as well because

if you have drugs --- resistance.

(Slide.)

And then, sort of the philosophical approach, you know. Fred Angulo --- do something now, and the attitude is that until we do something --- be done with it and --- just to make some groups happy or do we do nothing and say it's too hard, or do we look at it in terms of thirty years and say, we need to treat the sick animals.

We have to be humane --- resistance will develop so let's start taking steps --- steps at a time. We'll first look at the environment and establish where we are in terms of --- resistance --- gap there and to develop --- and use --- fish pathogens that ---

(Slide.)

But again, you've got the big --- gap and so, what I'm saying, take a step back and don't try to give people the answer tomorrow of what you need for your pre-approval studies but look at it in terms of --- we've got to find out what's on the environment, in the land and in the water, to develop --- and to identify --- I mean, people are just --- to start to look at fish --- in water for all sorts of bugs which are not that easy --- and somebody's got to pay for it and I think that we ---

CHAIRMAN MacMILLAN: Okay. So --

DR. REINSCHUESSA: We are melting.

CHAIRMAN MacMILLAN: We're not --- I like your stuff there. Any suggestions on where to go from here?

DR. REINSCHUESSA: For the next hour ---

CHAIRMAN MacMILLAN: Well, yeah. We have to make some report to the group this afternoon, but ---

MS. ORIANA: Well, I missed yesterday but --- on choice of organism ---

CHAIRMAN MacMILLAN: Yeah. We --

DR. REINSCHUESSA: Do you have some suggestions?

MS. ORIANA: No. Well, I'm confused --- in the water, on the fish or in the fish? Fish slime has ---

DR. REINSCHUESSA: Fish. In what critters? In what fish?

MS. ORIANA: Stuff out of the bay ---

CHAIRMAN MacMILLAN: The problem here is that the bacteria that are on the skin or are in the GI tract are going to be whatever's in the water basically.

MS. ORIANA: Well, I don't -- do you really think salmonella is ---

CHAIRMAN MacMILLAN: Well, that's a question. We don't know.

DR. REINSCHUESSA: Well, from what I've read, and I brought a couple of those articles with me -- there's some recent studies in Spain. There are transients. There are residents. They are not always the ones that are in the water

but some of them are and there are changes in the species. For example, they looked at trout and pike and they found different bugs in their guts and they found percentages and --- in one species of fish versus another.

CHAIRMAN MacMILLAN: From the same environment?

MS. ORIANA: Well, it's coming --

DR. REINSCHUESSA: Salmonella?

CHAIRMAN MacMILLAN: That would be different than ---

DR. REINSCHUESSA: Yeah, it is. It is different.

DR. KAZDA: --- different in some fish ---

(Simultaneous conversation.)

DR. REINSCHUESSA: And they were looking at the trout which were different from the ---

CHAIRMAN MacMILLAN: It was just brought up ---

DR. REINSCHUESSA: These were wild --- trout and wild pike. They recently, the same --- recently did another study which I only have the abstract of --- it's not that simple, let's put it that way. In a pond, you might end up with more bugs --- again, if you have larger number of bugs in that environment, then maybe your fish --- will be more --

CHAIRMAN MacMILLAN: About fifteen years or so ago --- we looked at --

DR. REINSCHUESSA: I've got that paper, too.

CHAIRMAN MacMILLAN: Okay. But that was long after --

DR. REINSCHUESSA: People --- intestinal flora ---

CHAIRMAN MacMILLAN: I think that work was done sometime in the '80s because there was a large --- so we collected fish throughout the year and one thing we didn't do was look at the --- which was too bad because that would be interesting to look at.

I think that that --- and generalizations about what is happening in the population on microbial flora in the GI tract. The skin, I don't know if very many people have looked at the skin.

MS. ORIANA: I had a master's professor who -- I mean, that was his thing.

DR. REINSCHUESSA: Characterizations --- some studies on aquaculture, striped bass and research systems and --- systems and they found something similar to what you're saying --- shows a lot different. So, you know, if we're talking pre and we've got, you know, fifty aquaculture species and god knows what else out there in the environment, and so, I don't think that the answers are really readily obtainable.

MS. ORIANA: I'm just trying to understand what people are --- just that they found the same ---

DR. REINSCHUESSA: And they found some ---

MS. ORIANA: Right.

DR. REINSCHUESSA: But a lot of this stuff -- a lot of the bugs --- characterized in terms of ---

DR. BUTLER: And it's likely that of all the species, just like terrestrial species, have a different collection of flora, period, and it varies within the species and between species but it doesn't mean that you shouldn't perhaps look at, you know, trying to characterize -- and I just say that research would contribute to that.

DR. REINSCHUESSA: You need to develop the model

DR. BUTLER: Yes.

DR. REINSCHUESSA: If you are going to ask people to use.

DR. BUTLER: Yes.

DR. REINSCHUESSA: And we can't just ---

MS. ORIANA: Are you saying that the focus in on --- bacteria and you were saying ---

CHAIRMAN MacMILLAN: Well, that was just --

MS. ORIANA: I guess I'm confused.

CHAIRMAN MacMILLAN: Well, the reason I suggested human, because that's the most --- concern. The other things, and this gets to the innocent bystander issue, is that --- can go from --- risk from --- aquatic environment to people --- that we don't have a way to measure what that is, from my perspective.

So if we just focus on the human pathogens, because that's clearly --- that has a greater probability of being an issue --- than say aeromonas --- but we don't have a way to

measure that. See, because you get to the aquaculture, it brings more than just --- and people come in contact with --- species.

Should there ever be --- then the issue's going to be almost the same as for the --- species, only the difference being that most people don't eat --- some people do but most people don't and they're --- that's the only difference between ---

The carp was just ont an item that most Americans eat --- in Asian markets.

DR. KAZDA: That was when I lived in Ontario --- steel mills ---

DR. SIMMONS: If I recall, the data presented by Tom Bell at various meetings, the tonnage of carp in Southeast Asia far outweighs --- salmon, trout --- is tremendous, but usage of antimicrobial agents and so forth is probably extremely low because it's such extensive versus intensive.

CHAIRMAN MacMILLAN: Right.

DR. SIMMONS: It shocked me when I saw it.

CHAIRMAN MacMILLAN: So --

MS. ORIANA: Well I guess I see that as the first --- decision tree in the survey as to which way to go. Looking at --- bacteria or ---

CHAIRMAN MacMILLAN: Well, from my perspective, I want to kill two birds with one stone, focus in on human

pathogens --- and do the test and it's in vitro and --- systems, whatever it is, look at those because those are going to be more --- and a greater probability of infecting people than innocent bystanders.

Innocent bystanders --- a lot of work to do to find out what they are --- so we know that at least in some aquatic systems, the human pathogens are there. To take Fred Angulo's position, why not look at those first.

DR. SIMMONS: Well I was thinking last night about the decision tree, how you would use this and kind of think of examples and if you're using mutation frequency as one of the first decision points, what's a good example of that and Rifampin is a perfect example of that because the mutation frequency -- and don't write this down because I don't know if the number is correct, but I think it's less than ten to the sixth, which is a red flag.

And that has been weighed out in clinical usage, resistance with Rifampin develops quite rapidly if not used in combination with another agent. So they would be whatever number is picked and a mutation frequency, there's a red flag that would immediately cause concern about the use of this agent.

Most pharmaceutical companies wouldn't develop one that had a high mutation frequency because they know what the issues are and what -- that's a -- would be part of the data

package and as they're readily available decision point and should CVM, BBD, whoever looks at this, we better look at this carefully. And, you know, again, it's risk assessment.

But I don't -- I still have difficultly knowing what organisms to jump into. I certainly wouldn't have any problem with developing sensitivity patterns for the target organisms as well as the potential human organisms, but I don't know what to do with it beyond that.

DR. BUTLER: Well, why don't you put forward both those possibilities? I mean, if you're going to look at things, the target organism and a human pathogen -- because you're going to do the target organism, obviously, anyway.

DR. REINSCHUESSA: And those are the ones that are going to hopefully show up in clinical labs.

DR. BUTLER: Right.

DR. REINSCHUESSA: You could do some, you know, post-surveillance --- but I still think that if you're worried about transfer via environmental --- then that's not just aquaculture; that's --- with other groups, too. You're going to have to look at some nontarget drugs if you're worried about that --- transfer.

DR. SIMMONS: If you look at say the CECA program in Europe right now, they're not looking at sensitivity patterns for veterinary antimicrobial agents. They're looking at sensitivity patterns in the smaller carcass --- human pathogens

in this surveillance and NARMS is the same way. And I don't know if an aquaculture is included in that.

DR. BUTLER: But that leaves out of the picture what happens to the stool from those cattle spread on those ---, doesn't it?

DR. SIMMONS: Spread on what?

DR. BUTLER: Spread on the spouts and the other vegetables. It's just another piece of the whole continuum of antimicrobial resistance passing. It covers the food side, the carcass culture, but it sort of leaves that piece of almost still being spread everywhere and --- more food-borne illness from vegetables and I'm sure that's the same here than from meat.

DR. SIMMONS: That goes back to the environmental --- package.

DR. BUTLER: Yeah, exactly.

DR. SIMMONS: Because run off --

DR. BUTLER: All of those things.

DR. SIMMONS: All of those things are issues and there are specific means of evaluating those things right now, again, if I remember -- you know, what's happening to those residues.

CHAIRMAN MacMILLAN: Okay. Well it sounds like there's some agreement that if we do any passing on bacteria, that we ought to choose target --- than human pathogen ---

DR. BUTLER: Well, Renada will wants the others and it's a good thing she wants that information. Yes? And if you would ---

DR. REINSCHUESSA: In the short term, right now, that's what we can do, and that if we want to look at the effect on nontargets, then it has to be ---

CHAIRMAN MacMILLAN: But in terms of being part of the pre-approval package -- is that --- the approval studies, would you insist that that be done as well?

DR. REINSCHUESSA: It depends on what time frame you're talking about.

CHAIRMAN MacMILLAN: Well, if you --

DR. REINSCHUESSA: If you start -- if you say we want to start setting up a pre-approval study in the next six months, the ones that you --- are going to have to be those organisms that you mentioned, human pathogens and --- but if we're looking to refute --- we should leave ourselves that avenue --- and you may add other drugs -- bugs to your list.

(Laughter.)

CHAIRMAN MacMILLAN: In the wording of --- I guess you'll publish some sort of guidance. Is that how that happens?

DR. REINSCHUESSA: --- published.

CHAIRMAN MacMILLAN: You publish some sort of guidance on pre-approval studies?

DR. REINSCHUESSA: Is that what you're asking?

CHAIRMAN MacMILLAN: Yes.

DR. REINSCHUESSA: I'm sure.

CHAIRMAN MacMILLAN: Okay.

DR. BUTLER: No, but it's absolutely true. I mean, the information has to be got sooner or later to know what the real impact is across the board.

CHAIRMAN MacMILLAN: The one thing I can insist on, if you do for aquaculture, you have to do it for all the other --

DR. BUTLER: Oh, yes.

CHAIRMAN MacMILLAN: All the other agriculture industries that are using antibiotics. So it would be orchards, pet animal, all those things that we look at. You're going to put this into perspective --

DR. BUTLER: Yep.

CHAIRMAN MacMILLAN: -- you need to do that. So that's what the --- would have to do.

DR. BUTLER: We have those on our list in our little group, federally, that's looking at it, everything from bees to whatever.

MS. ORIANA: And I know our environmental group is looking ---

CHAIRMAN MacMILLAN: So in terms of verbiage that we would suggest is that the --- but I guess that the antibiotic

resistance mechanisms of resistance development ---

DR. REINSCHUESSA: Look at profiles ---

DR. SIMMONS: Sensitivity profiles ---

CHAIRMAN MacMILLAN: So just sensitivity profiles of target organisms and human pathogens. We want selection of pathogens or ---

DR. SIMMONS: How about relevant?

CHAIRMAN MacMILLAN: Relevant.

MS. ORIANA: You always pick the ones -- basically the three or four big ones that you pick, although I don't know that people know if a campy is an issue. I mean, a lot of these things we don't know yet.

DR. REINSCHUESSA: And I think that's maybe a problem with trying to --- I mean --

DR. BUTLER: Right.

DR. SIMMONS: What organism would be a relevant organism for an antibiotic that's going to be developed for use in salmon and sea creatures?

CHAIRMAN MacMILLAN: Vibrio would be a relevant --- and ---

DR. REINSCHUESSA: And are you asking them to do it in --- studies with these or are you asking them just to ---

CHAIRMAN MacMILLAN: They're not going to be effective.

DR. SIMMONS: I wouldn't -- again, I'm trying to put

this in what's predictive -- if I sample water or fish or whatever, and I don't get those organisms out in that study, then they are --- if we just say, well, yes, in Egypt they picked this organism up and --- to me, if you can't get the organism from the test system that you're using, then using the relevant organism.

MS. ORIANA: The problem is the test system --- and the other thing is, I don't know ---

CHAIRMAN MacMILLAN: Well the temperature -- if you have salmonella in warm water temperatures --- it's not going to reproduce as fast as --- so, you know, relevance is the question. --- is it relevant? Is it predictive? And what was the third one?

DR. SIMMONS: Can it be validated or is it verifiable? Is that a word?

CHAIRMAN MacMILLAN: So if we suggested that -- well maybe we could do -- well, that's true. Maybe we can just say such as. I mean, you have to both your application and --- in Costa Rica. You could perhaps look at salmonella, or let's take shrimp --- and whether we produce it or not ---

(Comments off microphone.)

CHAIRMAN MacMILLAN: Well, what happened is --- as I understand it, they got --- it's not a food-borne --- and that's only been found once, not that it wasn't a serious issue; it certainly was. So would you necessarily use that ---

I don't know. And something that perhaps -- something you decide later on.

MS. ORIANA: And where is the listeria coming from? Just from runoff from the farms ---

CHAIRMAN MacMILLAN: Listeria monocytogenes, it's a pretty ubiquitous bacteria and seagulls carry it. Seagulls poop in the water --- whether it's reproduced or not, I don't think anybody's studied but in terms of trying to -- right now, the finished product in processed fish supposed to be all important --- zero tolerance in ---

MS. ORIANA: Don, why don't you --- essential or -- yeah ---

CHAIRMAN MacMILLAN: And to say, for example ---

(Break in tape.)

CHAIRMAN MacMILLAN: We wanted to highlight some of these unique features about -- of aquaculture because there really are some unique things that make this more difficult to --- and then -- so --- minor species. Somebody identified --- lots of places that resistant bacteria can reproduce --- that production system falsely.

DR. BUTLER: That's okay.

CHAIRMAN MacMILLAN: There's lots of places where bacteria can be reproduced from the production system.

DR. BUTLER: Do you really mean potentially resistant or inputs of human pathogens?

CHAIRMAN MacMILLAN: Well, both. You can get innocent bystander bacteria introduced and you can get human pathogens being introduced that the pathogens alone, by themselves without any thought of antibiotic response could be a problem, but certainly, this issue is the resistant. So, it can come from aquaculture practices or it can come from these different places here.

And the other item that's been unique about aquaculture is in this debate for the past two days, we've had limited, very limited public participation in the consideration of pre-approval study designs. So that's limited, somewhat, our ability to address some of these things and feel like we've really captured the best ---

Based on what we have, which is based on FDA, one private producer and one drug company representative, and one or two public interest groups who have come up with some ideas. Does that capture what we're after so far? Okay. We can go to the next slide maybe.

(Slide.)

There are some consequences to our limited antibiotics. Again, we only have two. One thing that happens is that you put increased selected pressure on the bacteria that are there that are exposed to the two drugs, potentially exposed to the two drugs that we have and they could increase the probability of resistance.

That could be remedied by better ability to rotate the drug choices in those systems. So it's a real disadvantage, obviously, to have just two antibiotics. You know, the down side to that is there will be groups, perhaps even in our own midst, who believe that there should not be any antibiotics for aquaculture.

DR. GOTTHARDT: But you know, there --- the species.

CHAIRMAN MacMILLAN: That's true.

DR. GOTTHARDT: Because the two that are approved are only approved for --- particular indications and --- species.

CHAIRMAN MacMILLAN: --- species, yeah.

DR. GOTTHARDT: And because they're in the feeds, --- produces --- viable option.

CHAIRMAN MacMILLAN: FDA --- decide on that proposed ---

DR. GOTTHARDT: FDA has gotten the comments back ---

CHAIRMAN MacMILLAN: So they are going to be --- not just tabled or anything.

DR. GOTTHARDT: It's on the table.

(Slide.)

CHAIRMAN MacMILLAN: Okay. So then we were going into, trying to answer the questions that were on our agenda. What are the positive aspects of the study concepts presented and the thought here was to state that we redefined our own study concepts and then go through what those study concepts

are. So maybe if we could go to some of the other slides to capture what has already been put down like --- yeah, I think these are ---

(Slide.)

CHAIRMAN MacMILLAN: Well the one thing we need to capture is this idea of high use --- regulatory action, high use versus low use, the binaries. But let's go to the other thing first. Okay. ---

DR. REINSCHUESSA: Where are the three --- relevance and --

CHAIRMAN MacMILLAN: Right. Right.

DR. REINSCHUESSA: That's the one I thought you were trying to put into that ---

CHAIRMAN MacMILLAN: Go back to slide source.

DR. REINSCHUESSA: Its relevance and --- are these the study concepts?

CHAIRMAN MacMILLAN: Well, it's not so much --

MS. ORIANA: What does study concepts mean?

CHAIRMAN MacMILLAN: Yeah. Why don't we just eliminate that question. Let's eliminate that question and just put in, these are the things that we considered important for whatever studies we have -- we decided to suggest, something like that.

DR. SIMMONS: Okay. So we are going to insert this slide where we have --

CHAIRMAN MacMILLAN: Yes.

DR. SIMMONS: --- Tom Shyrocks --- so the last slide we're going to insert with this one.

CHAIRMAN MacMILLAN: Right. Just replace it.

DR. REINSCHUESSA: Or you could just say that this is what we're using to address that. I don't know if you want to dump it completely or just say, this is how we're addressing it.

CHAIRMAN MacMILLAN: Well, let's just dump it.

DR. REINSCHUESSA: Okay.

DR. SIMMONS: I don't think it makes sense --- to make this flow from the last slide, I think you need to retitle it or --

CHAIRMAN MacMILLAN: Yeah, what is the last --- so the things that we considered discussing what would be appropriate for pre-approval studies are, and then the next slide is this one.

DR. SIMMONS: Let me find another word for factor here. Is the study parameter relevant.

CHAIRMAN MacMILLAN: Okay.

DR. GOTTHARDT: I am going to throw something out -- in the antimicrobial --- impact on human health --- pre-approval studies necessary for --- do we need pre-approval studies for antimicrobial resistance for all --- or are there some, potentially --- studies.

CHAIRMAN MacMILLAN: --- in the agenda, in some of the literature that I received --- pre-approval studies are only ---

DR. GOTTHARDT: I guess --

CHAIRMAN MacMILLAN: But that's in the literature.

DR. REINSCHUESSA: As much as I'd like to say --- the question would be is the potential for development of resistance --- do you know that is --- see what I mean? So you have to do the study in order to say the --- potential is --

DR. GOTTHARDT: I think it goes back to the drug --- and how bad it is to human health --- and how valuable it is to human health. Obviously, if you're talking about fluoroquinolone, then that is extremely important for human health. You might have another --- and that really doesn't have the same --- and there might not be --- human consequence there. I don't know. I'm just throwing that out. Do you want to think about it or --

CHAIRMAN MacMILLAN: It would seem that the agency is always going to have that discretion, I think.

DR. GOTTHARDT: Well, that may be what's behind the class III --- I don't -- the volumes between classes --- so that's why it's hard to say one particular drug is going to fall into one particular class.

But at the end of the day --- it's decided that a particular set of --- would fall into a class III or --- I

don't know. I don't think all that --- but there may be certain --- that we don't have --- but will there be some where we don't need pre-approval studies for antimicrobial resistance?

CHAIRMAN MacMILLAN: Well it doesn't hurt to throw it out.

MR. PRATER: That point would sure help us in aquaculture and it ties into the last slide, I think.

DR. GOTTHARDT: Because those might be the ones that, you know --

MR. PRATER: Yeah, if we move that to the first bullet, that will make a nice tie-in to the last slide. You can say, aquaculture is unique. Here are problem situations that we only have two drugs approved and, you know, do we -- if the drug candidate doesn't have this potential, do we need to raise the bar or can we lower the bar?

CHAIRMAN MacMILLAN: Right.

MR. PRATER: So we can just move this one up a bullet right now and make the transition -- so that maybe this first bullet could be the third.

CHAIRMAN MacMILLAN: Could you put, have significant potential or is that --

MR. PRATER: Yeah, that's true.

CHAIRMAN MacMILLAN: Can we go like this (indicating.) What a comedian. Okay. I thought on this one,

what study parameters are relevant? We're really trying to ask the question of what study parameters must be relevant --- do we want to go through to answer all these questions or do you want to just go with what we came up with?

MS. ORIANA: I mean, do they answer the questions ---

CHAIRMAN MacMILLAN: They are just suggested ---

DR. REINSCHUESSA: I think some of our slides ---

CHAIRMAN MacMILLAN: Yeah, they do.

DR. GOTTHARDT: And I will mention that Bill Flynn did ask how are you coming along with the questions.

DR. REINSCHUESSA: Well, we could just put up that one and say this -- get the next slides in --

MR. PRATER: So do we have another slide --- another slide to put in?

CHAIRMAN MacMILLAN: Well --

DR. REINSCHUESSA: Wait a minute. Back up. Combine slide one with slide two and three and then put something -- put in a slide that addresses those --- the factors --

CHAIRMAN MacMILLAN: So why not just move those --

DR. REINSCHUESSA: The factors and the data --

CHAIRMAN MacMILLAN: Move this question up here, two and three, and this is what we -- these are the things that we thought were important for daily microbial ---

MR. PRATER: So are we combining the concepts of the study factors --

CHAIRMAN MacMILLAN: Well, no. The slide will just show question two and question three and then, I think we have a slide -- well, maybe that's where we could introduce --- resistance development --- mutation. Well, whatever was on the list. Mutation frequency, mechanisms of resistance -- is that fair?

MS. ORIANA: I'm confused on the --- can we go back and see ---

DR. REINSCHUESSA: Well, what we did --

CHAIRMAN MacMILLAN: No.

MS. ORIANA: Oh, all right.

DR. REINSCHUESSA: We're using steps that we had ---

CHAIRMAN MacMILLAN: We haven't gotten to -- well are we going to, after these two questions, are we going to insert the mutation slide, this one?

MS. ORIANA: --- just to get it closer ---

MR. PRATER: Okay. Question number two, what role could the various types of data --- in evaluating microbial effects?

CHAIRMAN MacMILLAN: So make the title just types of data?

MS. ORIANA: Well, the question is what can we do.

DR. REINSCHUESSA: I thought this one was mostly more number three than number two.

MR. PRATER: Number three, what factors should be

considered and they have the information about species, water quality parameters. I think that's what we were asking in three, though. Various types of data.

DR. REINSCHUESSA: Your know, these questions ---

MR. PRATER: Well, they may not address what we need. Well, they may not address the issue in its totality but I think they do sort of address what we need as regulators and I don't think we're trying to solve the problem as much as we're trying to figure out what we need to do in the context of pre-approval studies.

What can be gained with pre-approval studies? And Bob suggested that these are things that -- data, types of data that are typically generated and may help us answer some questions about antimicrobial resistance. So I think this is a reasonable answer to question number two and could help us develop a pre-approval process.

DR. GOTTHARDT: Maybe we are suggesting --- that this type of data be collected?

CHAIRMAN MacMILLAN: Yep.

DR. REINSCHUESSA: The role that the data would play, I mean, to me, that sort of seems a little bit of the goal side. I would --- what are we going to do -- to me, the question is sort of saying, you know, what is the data going to tell us when we would use it? If it doesn't roll with various types of data --- evaluating microbial ---

MR. PRATER: I think these are the types of data that are out there --- and another question could be, the current data are not sufficient, then what data types do we need? And this is being put forth as types of data that are out there may be helpful in the context of pre-approval studies to help us address this.

I guess, ultimately, I thought that's where we were going, is we were going to sort of define what we wanted to what is available in the context of pre-approval studies and suggest that, you know, how that could be used as a basis for post-approval monitoring.

What types of data are currently available in the context of pre-approval studies that could help us form a foundation or basis for performing, monitoring new -- I think we accepted, either later yesterday or early today, that the bulk of this problem would be done in the post-approval phase. Really, the only good way we have, based on all --- predictability is to monitor these things in the post-approval phase.

So if we back up and we look at pre-approval, well, is there anything that we can take from the pre-approval? Is there anything we can modify --- we can't put a lot of new requirements on it because I don't think they're going to get us anywhere because we had all these problems with predictability.

What's available now? Are there additional types of data that we could ask for that would reasonably give us some foundation for examining this in post-approval?

CHAIRMAN MacMILLAN: So shall we eliminate question three or move question three?

DR. GOTTHARDT: You know, because aquaculture is kind of unique, I don't think we'd want to eliminate --- some of the factors are ---

CHAIRMAN MacMILLAN: Oh, yeah. I wasn't thinking of eliminating, just moving it.

MR. PRATER: It can precede this slide with question number two and then we can make another slide ---

DR. REINSCHUESSA: Do we want to add ---

MR. PRATER: I'm going to retitle it.

DR. REINSCHUESSA: Factors to consider because that goes along ---

DR. GOTTHARDT: Do we want to elaborate a little bit on the type of aquaculture? I know what we mean by that, but do we want to say type of aquaculture --- system or something, just to -- for folks that aren't maybe ---

DR. REINSCHUESSA: Randy did that pretty well when he introduced it on Tuesday. But it doesn't hurt to reiterate. Or actually, if you just put type of aquaculture and then parentheses, put in closed or open, sort of list some of those ---

CHAIRMAN MacMILLAN: I'd put ponds, net pens, raceways.

DR. REINSCHUESSA: Take out open and leave closed.

MR. PRATER: We say water type but we really talked about water quality parameters and we have talked about other inputs into different systems in the previous slide. Do you want to get rid of this and insert water quality parameters?

CHAIRMAN MacMILLAN: No, I wouldn't. Under water type, we could just put --- put water quality. We could almost leave number four the way it is and add our list -- and then perhaps in response to question five, we could identify what are long term research needs are or something like that. Would not become part of the pre-approval package at this point.

DR. REINSCHUESSA: I guess, to sort of throw a monkey wrench into --- to go back to the slide talking about --- on human pathogens --- I'd consider just putting in --- specific species but just saying nonfood --- pathogens because there are a fair number that we might need to consider.

CHAIRMAN MacMILLAN: Microbacteria ---

DR. REINSCHUESSA: I mean, I don't necessarily want to go into each ones, but I wanted to put that as another possible pathogen for certain species that might be important to ---

CHAIRMAN MacMILLAN: So nonfood but --

DR. REINSCHUESSA: Put a question mark by it and give

it some thought.

CHAIRMAN MacMILLAN: Human health. Nonfood but human health?

DR. REINSCHUESSA: Nonfood safety for human health pathogens.

DR. REINSCHUESSA: I think the first point -- I thought that was one we wanted to do, to prioritize the list.

CHAIRMAN MacMILLAN: Yeah, why --

DR. REINSCHUESSA: Because with aquaculture, the uses are so much smaller than all the other stuff that's poured into the environment, that we want that in the factor as opposed to like EPA --- technically feasible to hit on this --- is it more difficult with the amount of --- pull out the last three and dump them.

MR. PRATER: This one, too?

DR. REINSCHUESSA: Yeah. We're trying to get away from necessarily mentioning --- how about this number one in a perfect concepts?

MR. PRATER: This one?

DR. REINSCHUESSA: But before you do it, let's see ---

DR. SIMMONS: How long do you have to talk, Randy?

CHAIRMAN MacMILLAN: You know, I don't think there is a time limit. It's 1:00 until -- the public comments -- until 3:00 and then all four groups.

DR. SIMMONS: --- only have the four groups.

CHAIRMAN MacMILLAN: And some groups will probably have more to say than aquaculture. And I imagine aquaculture will be last.

(Laughter.)

CHAIRMAN MacMILLAN: I know. It's this feeling of ---

DR. SIMMONS: You need to have him sitting right next to you while you're watching him so if you need to change the slides as --

CHAIRMAN MacMILLAN: Right.

DR. SIMMONS: -- things evolve.

DR. REINSCHUESSA: And are we using that statement --- I'm not -- to that statement, but then again, I think it's important to point out that our use is low, and so, you know --

CHAIRMAN MacMILLAN: Well, just say that there's a need to prioritize regulatory action. Of course, that could also make it look like we're doing it, too, so you ---

MR. PRATER: Make a new slide with this?

DR. REINSCHUESSA: Put it under concepts; that's fine.

CHAIRMAN MacMILLAN: So where are we in answering the questions?

DR. REINSCHUESSA: I think we're at other.

CHAIRMAN MacMILLAN: Okay. And that's where we're

going to talk about future non pre-approval research --- and I think we can capture that when we talk about the research needs.

DR. REINSCHUESSA: Right.

CHAIRMAN MacMILLAN: Because there you are almost trying to capture the need of some people to do something now. So, before that future, non pre-approval -- and then the goal, that ought to be the very last slide, perhaps.

DR. REINSCHUESSA: The three to five year goal?

CHAIRMAN MacMILLAN: No, this goal right here. Develop, use the results from pre-approval --- research studies to develop appropriate doses, strategies for post-market surveillance, design post-market surveillance program and adjust the management on the farm with that information. Again, the idea being to make the research efforts, whatever they are, relevant to the real world.

MR. PRATER: Perhaps you could even modify labeling at this stage in the post-market. You know, if it looks like MIC is going up, go back and maybe that would be a slide we would go back and revisit later.

DR. REINSCHUESSA: So stick label in there. You might want to put that under dosing. --- the use instead of revisiting --- or label. To instruct labeling and revise labeling?

(Simultaneous conversation.)

MR. PRATER: This slide is in the post-market period.

MS. ORIANA: So this is modifying?

CHAIRMAN MacMILLAN: Right.

DR. REINSCHUESSA: But the dosing strategies is actually a pre-market.

MR. PRATER: So should we --

DR. REINSCHUESSA: Where I was going from is what are we using the pre-market studies for? Part of it is when you're trying to develop your strategies or how do you dose the animals? We use those resistance parameters as part of your dosing outlines. And so that would affect labeling. And then --

MR. PRATER: Take this somewhere?

DR. REINSCHUESSA: Or you could put those -- you could have pre-market and then a couple of them in post-market.

CHAIRMAN MacMILLAN: And this could be refined dosing strategies --

DR. REINSCHUESSA: Right.

CHAIRMAN MacMILLAN: -- for the post-market goals. Refine dosing strategies.

MR. PRATER: Okay.

CHAIRMAN MacMILLAN: Presumably, you already know how to get a dose and that's what a lot of --- is for.

DR. REINSCHUESSA: But that's what the early work would be there.

CHAIRMAN MacMILLAN: Right.

DR. REINSCHUESSA: I mean, so those studies would -- the pre -- so I would split this slide under two parts -- use of the results, use of your pre-approval study would be one and pre-approval process, dosing regimes and labeling, and in the post-market, compare, you know, with -- use those pre-results to compare with your surveys in your farm ---

MR. PRATER: Then I would suggest that we take those topics and move them further up.

DR. REINSCHUESSA: Well we could make two slides.

MR. PRATER: Make two slides. Okay. So I am just going to cut this for now and we're going to make a new slide.

MR. PRATER: --- efficacy studies or something else. Can we quantify -- or qualify --- or is this just --

DR. REINSCHUESSA: Identify -- I think it might be, like under the areas of directions for use or limitations. If you were to identify --- in labeling -- for instance, on the fluoroquinolone --- put in statements that have to do with poultry litter, and that's kind of --- this kind of data, I think.

MR. PRATER: Okay. Does that capture that -- their words? Qualifying ---

DR. SIMMONS: We're making the assumption that those two --- are related to the goal of minimizing potential for --- resistance?

DR. REINSCHUESSA: That one should ---

DR. SIMMONS: Yeah, because --- and I think that was number four on Fred's list.

CHAIRMAN MacMILLAN: Uh-huh.

DR. SIMMONS: Optimizing dosing strategies.

DR. REINSCHUESSA: That's -- I guess maybe you need to expand it ---

DR. SIMMONS: Well, I mean, if you are going to talk to it, then if you're happy with the slide, that's fine.

DR. REINSCHUESSA: No, no. That's a good point.

DR. GOTTHARDT: Or maybe we want to replace develop with optimize because we ---

DR. SIMMONS: Right.

DR. REINSCHUESSA: To minimize dosing strategies to minimize resistance.

DR. SIMMONS: So we --- fluoroquinolone dosing strategies have changed over the past five years. It's quite significant.

DR. REINSCHUESSA: With that goal in mind?

DR. SIMMONS: Well, I think we learn more about the effects, concentration effects ---

MS. ORIANA: What happened to number eleven? So it's not pre-approval or post-approval? It's ---

MR. PRATER: Take this out?

DR. SIMMONS: The concern there was we wanted to be

sure to identify --- pre-approval.

DR. REINSCHUESSA: Yeah, I would leave it in. Or you can, instead of --

MR. PRATER: Nonsponsor --

DR. REINSCHUESSA: Put another bullet and say this is not a requirement for sponsors. Is that what --- underneath that?

DR. GOTTHARDT: Then it is not.

DR. REINSCHUESSA: I mean, I am not asking --

MR. PRATER: We haven't earlier absolved this sponsor in the post-market days --- development model --- on this side ---

CHAIRMAN MacMILLAN: Why don't we go with the slide order and see how things fit.

DR. BUTLER: --- pre-approval study, this might provide a positive for the sponsor in terms of, well, this drug would seem to, in that species, cause antimicrobial resistance but thanks to our study that we did in pre-market approval, we can show that this species and this were not affected.

So that could be a positive for the drug sponsor and good information for the reviewer who might be stuck saying, well gee, we won't really know if that's causing antimicrobial resistance and should we approve that for this species? And, just a thought for ---

DR. SIMMONS: Could you go back one, please.

CHAIRMAN MacMILLAN: Are we going to do pre-approval studies with --- model?

DR. BUTLER: That's what you're here to do, put together a suggested animal study model.

CHAIRMAN MacMILLAN: Right. But when we go to the next slide, we're not -- our thoughts so far have not been to require a model at all. We're answering the question but we haven't looked in -- identified --

DR. REINSCHUESSA: The header is wrong for where we're at, yeah.

CHAIRMAN MacMILLAN: Yeah.

MR. PRATER: Do we want to modify this slide?

DR. REINSCHUESSA: And then the study plan instead of model development. The study itself is the model for what --

CHAIRMAN MacMILLAN: Right.

DR. REINSCHUESSA: When I was thinking with this, I was thinking of modeling organisms but if it's --

CHAIRMAN MacMILLAN: And that's what we'll talk about later on.

DR. REINSCHUESSA: Right.

CHAIRMAN MacMILLAN: The research is develop that model system so that you can reasonably expect to predict what's going to happen.

MR. PRATER: Design okay?

CHAIRMAN MacMILLAN: Yes.

MR. PRATER: I think this is more of a ---

DR. REINSCHUESSA: I guess the one thing that I have considered --- mentioned and this goes for anything, not just aquaculture. If we're looking to see what's currently out there in terrestrial --- environments --- what's in the food, the organisms that are in those foods.

CHAIRMAN MacMILLAN: Nonpathogenic --

DR. REINSCHUESSA: The resistant bugs that are in the food.

MR. PRATER: You mean in the animal feed?

DR. REINSCHUESSA: Yes.

MR. PRATER: There could be.

CHAIRMAN MacMILLAN: There have been studies done where they found salmonella in fish feed. That was done twenty/thirty years ago.

DR. REINSCHUESSA: I think the rendering industry is beginning to look at some of that itself. --- but it is food for thought because, you know, if you're using the feed as the delivering system and what are the effects of some of these substances in the -- on those organisms -- they don't die during the processing.

CHAIRMAN MacMILLAN: Of course, these days, the feed gets so hot and under such high pressure. In --- days the feed was cold, wet, moist --- for example, but today it's --- or --- food in virtually all, at least catfish and trout, celmonids

--- so it's not likely that they will survive. And we've done some pasteurization and some tests with viruses and they don't make it through. So for virus testing ---

DR. GOTTHARDT: Randy, how comfortable are you with --

CHAIRMAN MacMILLAN: I'm pretty comfortable. We need to see the end. Is this the end?

MR. PRATER: Not quite the end.

CHAIRMAN MacMILLAN: If I miss something, there's no reason -- I think it's pretty -- it's not a formal situation so people can speak up ---

DR. GOTTHARDT: I won't be there.

CHAIRMAN MacMILLAN: Okay.

DR. SIMMONS: On your slide mechanisms from --- missing on that was mechanism of action.

DR. REINSCHUESSA: Mechanism of action of the drug?

DR. SIMMONS: Yes.

DR. REINSCHUESSA: Well, I was sort of forgetting all the routine stuff ---

MR. PRATER: Would you like to see ---

DR. REINSCHUESSA: We go through -- I mean, we didn't also mention that the chemical/physical properties --- in water.

DR. SIMMONS: That the mechanism of action is what we derive much of the attention it's going to get because if its

mechanism of action is made to an antibiotic that is currently reserved for --- then you're going to get some pretty high attention ---

DR. REINSCHUESSA: That sort of drives the mechanism of resistance.

DR. SIMMONS: For example, we have a drug on the human side that you wouldn't dream of touching it because of ---

CHAIRMAN MacMILLAN: So since this is aquaculture, do you want a blue background on it?

MR. PRATER: Yeah, I might go back and add background to all of these.

CHAIRMAN MacMILLAN: And the format?

MR. PRATER: It's amazing.

CHAIRMAN MacMILLAN: --- design down at the bottom.

(Discussion of graphic design; session was concluded.)